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Dementia Resulting From Traumatic Brain Injury

What Is the Pathology?

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Traumatic brain injury (TBI) is among the earliest illnesses described in human history and remains a major source of morbidity and mortality in the modern era. It is estimated that 2% of the US population lives with long-term disabilities due to a prior TBI, and incidence and prevalence rates are even higher in developing countries. One of the most feared long-term consequences of TBIs is dementia, as multiple epidemiologic studies show that experiencing a TBI in early or midlife is associated with an increased risk of dementia in late life. The best data indicate that moderate and severe TBIs increase risk of dementia between 2- and 4-fold. It is less clear whether mild TBIs such as brief concussions result in increased dementia risk, in part because mild head injuries are often not well documented and retrospective studies have recall bias. However, it has been observed for many years that multiple mild TBIs as experienced by professional boxers are associated with a high risk of chronic traumatic encephalopathy (CTE), a type of dementia with distinctive clinical and pathologic features. The recent recognition that CTE is common in retired professional football and hockey players has rekindled interest in this condition, as has the recognition that military personnel also experience high rates of mild TBIs and may have a similar syndrome. It is presently unknown whether dementia in TBI survivors is pathophysiologically similar to Alzheimer disease, CTE, or some other entity. Such information is critical for developing preventive and treatment strategies for a common cause of acquired dementia. Herein, we will review the epidemiologic data linking TBI and dementia, existing clinical and pathologic data, and will identify areas where future research is needed.

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Traumatic brain injury (TBI) has beleaguered humanity from its inception, being among the earliest illnesses described in human history.[1] A South African australopithecine skull estimated to be 3 million years old shows evidence of a lethal skull fracture administered by another early hominid,[2] and skull fractures are very common in *Homo erectus* skulls found throughout the world. Recent quantitative studies from burial sites of prehistoric modern humans[3,4] indicate that approximately one-third of our ancestors experienced cranial trauma sufficient to result in a skull fracture. This high rate of TBI in prehistoric humans makes it likely that genetic variants that confer resistance to brain trauma, or foster repair and plasticity of injured neural tissue, would have been selectively favored through evolution.

Traumatic brain injury remains a major problem in modern societies, primarily as a consequence of traffic crashes and falls. In the United States alone, an esti-

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14. ABSTRACT

Traumatic brain injury (TBI) is among the earliest illnesses described in human history and remains a major source of morbidity and mortality in the modern era. It is estimated that 2% of the US population lives with long-term disabilities due to a prior TBI and incidence and prevalence rates are even higher in developing countries. One of the most feared long-term consequences of TBIs is dementia, as multiple epidemiologic studies show that experiencing a TBI in early or midlife is associated with an increased risk of dementia in late life. The best data indicate that moderate and severe TBIs increase risk of dementia between 2-and 4-fold. It is less clear whether mild TBIs such as brief concussions result in increased dementia risk, in part because mild head injuries are often not well documented and retrospective studies have recall bias. However, it has been observed for many years that multiple mild TBIs as experienced by professional boxers are associated with a high risk of chronic traumatic encephalopathy (CTE), a type of dementia with distinctive clinical and pathologic features. The recent recognition that CTE is common in retired professional football and hockey players has rekindled interest in this condition, as has the recognition that military personnel also experience high rates of mild TBIs and may have a similar syndrome. It is presently unknown whether dementia in TBI survivors is pathophysiologically similar to Alzheimer disease, CTE, or some other entity. Such information is critical for developing preventive and treatment strategies for a common cause of acquired dementia. Herein, we will review the epidemiologic data linking TBI and dementia, existing clinical and pathologic data, and will identify areas where future research is needed.

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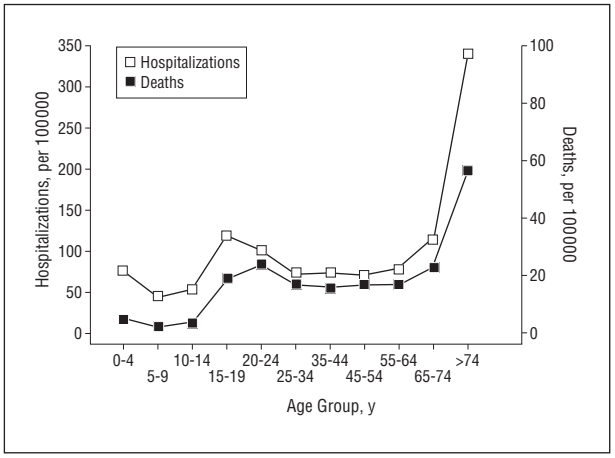

Figure 1. Annual rate of traumatic brain injury–related hospitalizations and deaths, by age. Adapted from Faul et al.[5]

mated 1.7 million people sustain a TBI annually, of which 275 000 require hospitalization and 52 000 die.[5] Rates are even higher in developing countries.[6] Traumatic brain injury is the leading cause of death and disability for persons between the ages of 1 and 44 years, and an estimated 5.3 million Americans, almost 2% of the population, live with long-term disabilities due to a prior TBI.[7] The segment of the population with the highest rates of TBI hospitalizations and deaths is elderly individuals (**Figure 1**). In young children and elderly individuals, falls are the primary cause of TBI hospitalizations and deaths, while traffic crashes are the primary cause in adolescents and young adults.[5]

TBI AS A RISK FACTOR FOR LATE-LIFE DEMENTIA

Traumatic brain injury is perhaps the best established environmental risk factor for dementia. A meta-analysis of 15 case-control studies[8] estimated that individuals who had had a head injury of sufficient severity to result in loss of consciousness were at approximately 50% increased risk of dementia compared with others (pooled odds ratio [OR], 1.58; 95% CI, 1.21-2.06). In the MIRAGE study,[9] where information on head injury was collected by interview of multiple informants and review of medical records, the OR for dementia was 4.0 (95% CI, 2.9-5.5) for head injury with loss of consciousness and 2.0 (CI, 1.5-2.7) for head injury without loss of consciousness. All these case-control studies have potential recall bias, an inherent limitation of the retrospective design. However, there is 1 prospective study on this issue that provides convincing data on the association between TBI in early to midlife and late-life dementia. Plassman et al[10] identified 548 US Navy and Marine veterans hospitalized for TBI in the Pacific theater during World War II. Controls were 1228 veterans hospitalized for non-TBI injuries at the same time. Study subjects were evaluated by telephone interviews and clinical assessments 50 years after the injury. The veterans who had sustained a severe TBI (defined as loss of consciousness or posttraumatic amnesia lasting longer than 24 hours) were more than 4 times as likely to have dementia compared with controls (hazard ratio [HR], 4.41; 95% CI, 2.09-9.63), while those who had sustained a moderate TBI (defined as loss of consciousness or posttraumatic amnesia lasting longer than 30 minutes but less than 24 hours) were at more than doubled risk (HR, 2.39; 95% CI, 1.24-4.58). No increased risk was evident for the veterans who had a mild TBI (loss of consciousness or posttraumatic amnesia fewer than 30 minutes). On the basis of these and other studies, an Institute of Medicine committee recently concluded that

> there is sufficient evidence of an association between moderate and severe TBI and dementia . . . limited/suggestive evidence of an association between mild TBI (with loss of consciousness) and dementia . . . [and] inadequate/insufficient evidence to determine whether an association exists between mild TBI (without loss of consciousness) and dementia.[11(p214)]

Available data allow a rough calculation of how much of the population's burden of dementia is attributable to TBI. Assuming that the cumulative lifetime incidence of TBI requiring hospitalization is 10%, a reasonable estimate based on the New Zealand Christchurch Health and Development Study[12] and a population-based telephone survey in Colorado (G. Whiteneck, PhD, unpublished data, 2012), and given that the relative risk of dementia in individuals who had a TBI of sufficient severity as to require hospitalization ranges from 1.5- to 3-fold,[8-10] the attributable risk of dementia to TBI is in the range of 5% to 15%.[13]

Several investigators have studied the relationship between inheritance of an apolipoprotein ε4 (*APOE* ε4) allele and dementia after TBI. In a population-based study in Northern Manhattan, New York,[14] a history of TBI and inheritance of an *APOE* ε4 allele were associated with a 10-fold increased risk of dementia, while *APOE* ε4 in the absence of TBI resulted in only a 2-fold increased risk. This study did not find an increased risk of dementia due to TBI in the absence of *APOE* ε4. Similarly, in the prospective study on World War II veterans,[10] there was a nonsignificant trend toward higher dementia risk in *APOE* ε4 carriers. On the other hand, in the MIRAGE study,[9] the risk of dementia was higher in those lacking the *APOE* ε4 allele (OR, 3.3) than in *APOE* ε4 heterozygotes (OR, 1.8) or homozygotes (OR, 1.3).

Little information can be gleaned from the epidemiologic studies regarding specific clinical features of dementia associated with TBI. Most studies have focused on Alzheimer disease (AD), and in the better studies,[8-10] the diagnosis of probable or possible AD was made using established National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[15] However, pathologic confirmation of AD was rare, and no information was available about signs and symptoms such as depression, agitation, irritability, and parkinsonism, which are typical of other dementing disorders that may overlap or coexist with AD.

NEURODEGENERATIVE PATHOLOGY AFTER TBI

In rodent models, TBI results in neurodegeneration and progressive brain atrophy that continues at least 1 year after injury.[16,17] Several proteins associated with neuro-

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degenerative disease in humans have been demonstrated to accumulate following experimental TBI in rodents. Amyloid precursor protein is upregulated immediately after TBI[18] and β-amyloid peptide accumulates over weeks and months.[18-20] β-Secretase, presenilin 1, and caspase 3 also accumulate up to 6 months after injury.[19] In triple transgenic mice expressing pathogenic mutations in amyloid precursor protein, presenilin 1, and tau, TBI results in accumulations of intraaxonal β-amyloid peptide and hyperphosphorylated tau, which persist up to 1 week after injury.[21] These findings have led to the hypothesis that β-amyloid peptide and tau accumulation are important mechanisms in the long-term neurodegenerative effects of TBI.[22] This hypothesis has important therapeutic implications, as recent developments in AD therapeutics, such as anti–β-amyloid antibodies, inhibitors of β-secretase or γ-secretase activity, or other amyloid- or tau-targeted therapies[23,24] may potentially have roles in the management of TBI.

Human pathologic studies addressing the mechanisms of post-TBI neurodegeneration are limited. Diffuse β-amyloid plaques are found in up to 30% of patients who die acutely following TBI.[25] β-Amyloid accumulation is rapid and can be detected in tissue excised surgically within hours of injury.[26,27] In a recent autopsy study of 39 individuals who survived between 1 and 47 years after a single TBI,[28] β-amyloid plaques and neurofibrillary tangles (NFTs) were present in up to a third of patients with prolonged survival after a single TBI. Recent studies of retired professional athletes who had sustained multiple concussions and developed dementia reported prominent tau-immunoreactive NFTs and astrocytic tangles, but β-amyloid pathology was noted in less than half the cases. The distribution of NFTs differs from that seen in AD and represents a distinct pathology, termed *chronic traumatic encephalopathy* (CTE) (discussed in detail later).[29] It is unknown whether similar findings are noted in individuals who sustained a single moderate or severe TBI, a population several orders of magnitude larger than that of retired professional athletes.

Another line of evidence indicating that neurodegeneration after TBI shares some features with AD comes from imaging studies. Cerebral atrophy after TBI is not diffuse but rather regionally selective.[30] The regions of the brain that show most prominent atrophy after TBI, such as the hippocampus, amygdala, precuneus, and parietal and frontal cortices, overlap closely (but not perfectly) with regions of predominant β-amyloid deposition, decreased glucose use, and progressive atrophy in AD.[31] These findings may relate to common molecular mechanisms shared between AD and TBI-related neurodegeneration.

CHRONIC TRAUMATIC ENCEPHALOPATHY

Whereas the long-term consequences of a single episode of primarily moderate to severe TBI have only recently been recognized, it has long been known that multiple mild TBIs result in late-life dementia. This was initially recognized in professional boxers by Harrison S. Martland in 1928,[32] who described acute, early symptoms of staggering and disequilibrium, associated with mental confusion and signs of slowed muscular movement. At late stages, usually years after retirement, some former fighters would develop clinical signs and symptoms reminiscent of parkinsonism, such as tremors, unsteadiness of gait, and masked faces and, finally, mental deterioration. The term for this syndrome has been *dementia pugilistica*, but more recently CTE is used.

There is one carefully conducted study on the prevalence of CTE in retired professional boxers. In 1967, the Royal College of Physicians appointed A. H. Roberts to study late neurological sequelae of professional boxing. Within 2 years, he interviewed and examined almost all of the 250 retired boxers randomly selected from 16 781 professionals registered with the British Boxing Board of Control between 1929 and 1955.[33] Roberts acknowledged the wide spectrum of clinical presentations among individuals yet ascribed the diagnosis of traumatic encephalopathy to a composite clinical syndrome primarily involving the cerebellar, pyramidal, and extrapyramidal systems. The neurological syndrome ranged from mild forms with dysarthria, asymmetric pyramidal lesions, and disequilibrium to severe disability with ataxias, rigidity, tremor, and dementia. Of the 224 former boxers examined, 37 participants (17%) showed clinical evidence of central nervous system lesions. Given the strict case definition criteria used in this study, it is likely that this estimate is a lower limit of the true prevalence of CTE in retired professional boxers. Dementia or neuropsychiatric disorders, in the absence of prominent motor symptoms, were not qualifying diagnoses for CTE in this study.

Over the last several decades, several studies have further defined the risk factors for CTE. These include boxing for more than 10 years, participating in 150 or more bouts, history of knockout or technical knockout, and being a slugger who is difficult to knock out.[34] Chronic traumatic encephalopathy is believed to be rare in amateur boxers, but well-designed prevalence studies have not been done. Inheritance of the *APOE ε4* allele is associated with increased risk of CTE in boxers.[35]

Pathologic studies of CTE have lagged, and as recently as 2009, only 51 cases of neuropathologically confirmed CTE had been reported in the medical literature.[29] In an early article in 1973,[36] Corsellis et al examined the brains of 15 retired boxers, correlating antemortem clinical symptoms recounted by surviving family members with neuropathologic examinations. Cerebral atrophy was noted as a general trend. In addition, the brains often displayed enlarged lateral ventricles with fenestrated cavum septum pellucidum and atrophied fornices detaching from a thinned corpus callosum. The cerebellum showed marked scarring particularly in the tonsillar regions with demyelination and loss of Purkinje cells. Similar to other studies, NFTs, aggregates of misfolded, hyperphosphorylated tau proteins, were discovered. The NFTs presided in the substantia nigra, with no detection of Lewy bodies indicative of Parkinson disease. The NFTs were also spread diffusely throughout the cerebral cortex, with preferential deposition in the medial temporal gray matter with concomitant extensive neuronal loss. In stark contrast to AD, senile plaques were rarely observed and if present, in scanty amounts, with the exception of 1 patient who died at age 57 years. The authors concluded that several neurological features of the boxers corresponded to structural and biochemical

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changes in their brains. For example, those with memory loss showed disruption of the limbic pathways (eg, medial temporal lobe and fornix) and with parkinsonism, impairment of extrapyramidal pathways (eg, substantia nigra). The authors further contemplated the propensity for outbursts of rage or aggression, also noted in other publications, to be due to brain damage, although without precise anatomical localization.

Since the publishing of these seminal articles, CTE has been further studied and characterized as a distinct progressive neurodegenerative disease entity in the category of tauopathy. Tauopathies are characterized by dissociation of tau proteins from microtubules, which are hyperphosphorylated and aggregate to form NFTs, a process that presumably serves as the instigator of toxicity and cell death by unknown mechanisms. Chronic traumatic encephalopathy has been confirmed at autopsy in football, soccer, ice hockey, and other athletes in contact sports with inherent risk of subconcussive or concussive injuries.[29,37] In these pathologically proven cases, clinical features were ascertained retrospectively by interview of family members and review of medical records. The clinical onset of CTE can range from the second to the seventh decades of life, with early symptoms more typically detected in approximately the fourth decade. Characteristically, neurological deficits progressively exacerbate and expand in symptoms, often over several decades, consistent with a progressive neurodegenerative condition. Behavioral abnormalities are prominent, often formerly uncharacteristic to the person, such as abrupt mood swings with explosive rage, depression, impulsive acts, and substance abuse. Other complaints include difficulty sleeping, memory impairment, poor concentration, slurring of speech, signs and symptoms of parkinsonism, and, at late stages, dementia. Not infrequently, these patients end their lives.

At autopsy, the brain can show global atrophy, with thinning of the corpus callosum and enlarged ventricles and cavum septum pellucidum. There also exists a characteristic distribution pattern of NFTs unique to CTE. The NFTs tend to aggregate in the medial temporal cortex, hippocampus and parahippocampal gyrus, thalamus, mammillary bodies, amygdala, hypothalamus, and substantia nigra. The NFTs also preferentially amass in the depths of sulci and encompass small blood vessels and ventricles in an irregular, patchy distribution (**Figure 2**). In the neocortices, NFTs concentrate in the superficial layers II and III, differing from AD in which NFTs predominate in the deeper layers V and VI.[38] Also unlike AD, there is a paucity of neuritic plaques in CTE.[29]

RISK OF CTE IN COMBAT VETERANS

Recognition of the prominence of neuropsychiatric symptoms in CTE has rekindled interest in the organic basis of posttraumatic stress disorder (PTSD) in combat veterans. Posttraumatic stress disorder was first recognized after World War I, when it was termed *shell shock* in recognition of its association with exposure to high-intensity explosives.[39,40] Although the initial investigators in the field suspected an organic etiology of this condition, a commission convened by the British government after the war concluded that shell shock was "a convenient evasion of duty, if not disguised malingering"[41(pp17-18)] and that "no case of psycho-neurosis or mental breakdown, even when attributed to a shell explosion or the effect thereof, should be classified as a battle casualty."[41(p190)] Over the past 100 years, PTSD has been accepted as a common consequence of combat and, in the past few decades, recognized to merit awarding service-connected benefits through the Veterans Administration in the United States. However, the neurobiologic basis of PTSD remains elusive.

Posttraumatic stress disorder is common in combat veterans. Vietnam veterans have a 20% to 30% lifetime prevalence of PTSD, and 10% to 15% had the disorder 15 years or longer after returning from Vietnam.[42] A study of older World War II and Korean War veterans found that the prevalence of PTSD remained as high as 12% even 45 years after combat.[43] Among service members returning from the current wars in Iraq and Afghanistan, the prevalence of PTSD has been estimated as high as 17%.[44] There is a strong statistical association between self-reported mild TBI and PTSD. In a study of 2525 returning US Army infantry soldiers, 43.9% of those reporting a TBI with loss of consciousness met criteria for PTSD, compared with 27.3% of those reporting a TBI without loss of consciousness, 16.2% of those with other injuries, and 9.1% of those with no injuries.[45] There is also a strong association between the number of mild TBIs and PTSD risk.[46] Similar to TBI, combat-related PTSD is associated with a significantly increased risk of incident dementia (HR, 2.31; 95% CI, 2.24-2.39).[47] It remains undetermined whether the association between PTSD and TBI shares common pathogenesis.

Although shell shock and PTSD have been recognized for many decades, there is a paucity of neuropathologic information on this condition. Service members with PTSD often complain of irritability, memory problems, difficulty concentrating, headaches, and sleep disturbances, a symptom complex that overlaps with civilians after mild TBI and with professional athletes with CTE diagnosed at autopsy. These observations lead to the hypothesis that a proportion of combat veterans with PTSD actually have CTE. In support of this view, Omalu et al[48] report on a case of a 27-year-old US Marine Corps veteran who was diagnosed with PTSD before ending his life by hanging. During his 2 deployments in Iraq, he was exposed to multiple blasts, sometimes being within 50 m of the detonation. After his second deployment, he developed progressive cognitive impairment, memory disturbances, and behavioral and mood disorders and became dependent on alcohol. At autopsy, his brain appeared grossly normal, but microscopic examination revealed NFTs in anatomical locations that are consistent with the diagnosis of CTE. This pathologic observation needs replication in a larger number of military veterans.

CLINICAL AND PATHOLOGIC FEATURES OF AD VS CTE

Clinical research to define clearly the signs and symptoms of CTE is at an early stage, making definitive differentiation from AD difficult. A clinical diagnosis of CTE

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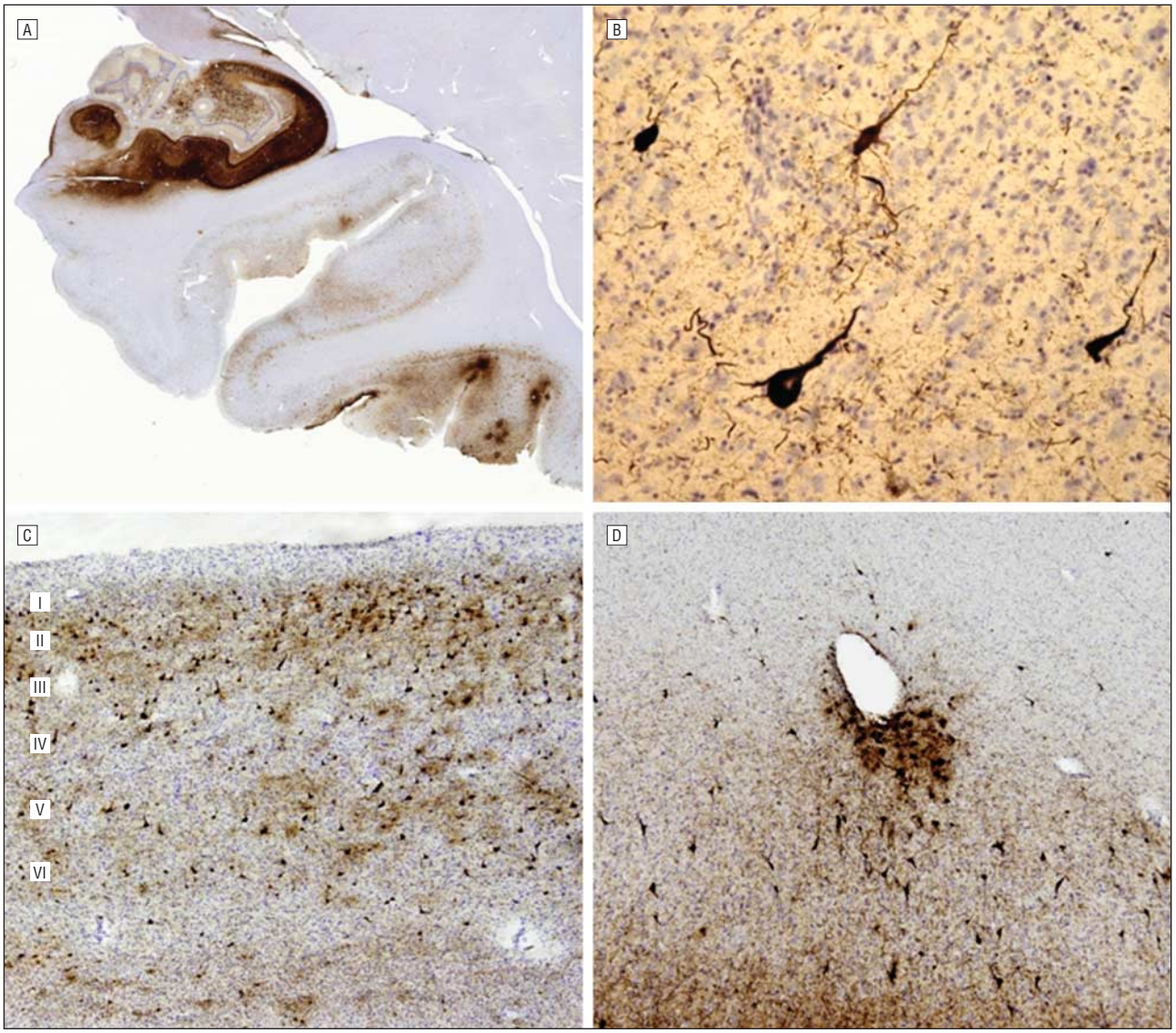

Figure 2. Histopathologic features of chronic traumatic encephalopathy in a former professional football player (courtesy of Ann McKee, MD, Center for the Study of Traumatic Encephalopathy, Boston University School of Medicine, Boston, Massachusetts). A, Scanning view of the hippocampus and parahippocampal cortex. Note intense immunostaining of the entire Ammon horn and subiculum with focal involvement at the depths of sulci of the inferior temporal lobe. B, Appearance of individual neurofibrillary tangles in the neocortex. C, Predilection for neurofibrillary tangle involvement in the superficial layers (layers II/III) (as opposed to deeper layers [layers V/VI], as is more common in Alzheimer disease) of the anterior insular cortex. D, Tendency for perivascular tau deposition and neurofibrillary tangle formation in the frontal cortex. All sections immunostained for abnormally phosphorylated tau (AT-8, monoclonal antibody that detects hyperphosphorylated tau, serine 202, and threonine 205). A, Original magnification ×1. B, Original magnification ×160. C, Original magnification ×30. D, Original magnification ×60.

should be considered for a patient with a history of TBI in conjunction with progressive central nervous system deterioration. History of prior head trauma is not often sought in the diagnostic workup of patients with dementia. Patients with CTE tend to present with chronic headache and more predominant behavioral and psychiatric features, such as depression, abrupt mood swings with explosive rage, and substance abuse, with an apparent inclination to engage in disinhibited, high-risk activities leading to early demise or blatant suicide. Dementia and parkinsonism trend toward a later appearance in disease progression. In a young adult or person of middle age, CTE as a diagnosis would be favored, given the infrequency of AD in this population. Nevertheless, CTE exists in persons of advanced age, and older individuals with dementia and a history of TBI may have a mixed dementia, with features of both CTE and AD.

Even today, AD is only definitively diagnosed at autopsy, with the identification of neuritic plaques and NFTs in the brain of an individual with an antemortem history of dementia. Chronic traumatic encephalopathy as yet does not have established neuropathologic guidelines, even though its predominant features have been sketched in the literature, as described earlier. The **Table** summarizes the distinguishing clinical and pathologic features between AD and CTE, which are supported by the available literature. These must be confirmed by larger prospective studies.

CONCLUSIONS AND AREAS FOR FUTURE RESEARCH

Traumatic brain injury is common in modern societies, and advanced neurosurgical and neurological care al-

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Table. Clinical and Pathologic Features Discriminating Between AD and CTE

	CTE	AD
Clinical		
Short-term memory deficits early in the course	+	+++
Depression early in the course	+++	+
Abrupt mood swings and explosive rage	++	±
Substance abuse	++	–
Parkinsonism late in the course	+++	±
Suicidal behaviors	++	–
Pathologic		
Global cerebral atrophy	±	++
Fenestrated cavum septum pellucidum	+	–
Neuritic plaques and β-amyloid deposits	±	+++
Neurofibrillary tangles in the neocortex	+++ Predominant layers II and III	+++ Predominant layers V and VI
Neurofibrillary tangles in the hippocampus and parahippocampal gyrus	+++ All sections of the Ammon horn	+++ Predominantly in CA1
Neurofibrillary tangles in the substantia nigra and locus ceruleus	++	±
Neurofibrillary tangles surrounding small blood vessels	+++	–

Abbreviations: AD, Alzheimer disease; CTE, chronic traumatic encephalopathy; +, mild; ++, moderate; +++, severe; ±, equivocal; –, absent.

low most victims of even severe injuries to survive for many decades, albeit sometimes with disabilities. One of the most feared consequences of TBI is dementia. Epidemiologic studies indicate that TBI in early to midlife is associated with an increased risk of dementia in late life, in the range of 2- to 4-fold compared with the general population. This risk appears to be much higher in the setting of multiple TBIs, although research in this area is in its infancy.

Understanding the features of dementia after TBI is critically important to society. While currently there are no effective therapies available to treat or prevent AD, several such therapies are in the horizon.[49] Studies in aging populations have been successful in identifying imaging and biochemical biomarkers of the early stages of AD,[50] information that is critical to the development and application of effective therapies. If TBI survivors are at increased risk of AD-type neurodegeneration, early recognition will be essential to implement preventive therapies. Alternatively, if TBI survivors experience dementia as a result of an alternate pathologic process, such as CTE, identifying early and preclinical diagnostic biomarkers is an essential first step for developing effective therapies. Finally, the recognition that certain members of society, such as military service members and professional athletes, are at particular risk of TBI-related dementia should stimulate research on preventive strategies focused on these individuals.

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